Doctopic: Analysis and Interpretation
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Aptara: Please add collaborator list

[A: We have edited your letter to avoid repetition, enhance readability, reduce length, and achieve consistency with Lancet style.]

Diagnosing psychotic disorders in patients with COVID-19

Authors' reply

We thank Dorothy Wade and colleagues and Mark Oldham and colleagues for their recognition of the cross-speciality effort of members of the UK's major professional neuroscience bodies who undertook this challenging UK-wide study during the exponential phase of the COVID-19 pandemic.[1] We also welcome the involvement of geriatricians and psychologists in future research.

We agree that delirium is common, especially in severe infections and in the intensive care unit. As stated in our Article, we acknowledge that the study might have under-ascertained [A: Could we rephrase to "not have recorded all such cases" or similar?] such cases. Changes in mental status with clear and recognised risk factors were not the focus of this study (eg, those explained by severe systemic illness and associated with dementia or cognitive impairment). We agree that if such commonly observed complications were included, they might have substantially increased the numbers [A: Please be more specific – the number of patients with delirium?], mirroring the situation in other critical illnesses. In this situation, the burden of CNS complications arising from COVID-19 would be even greater than we found in our study.

We agree that consistent terminology is needed for the many causes of alterations of mental state and an improved understanding of the underlying pathophysiology that should determine this is urgently required. We acknowledge the position paper on a proposed terminology of these complex presentations and, appreciating the value of multidisciplinary approaches, would support involvement of the professional bodies in relevant areas of psychiatry, neuropsychiatry, and neurological infection, as well as patient and public involvement, in future iterations.

We understand the motivations for wishing to avoid the term altered mental status. However, we carefully considered the information notified and took an ontological approach for over-arching terms that include disturbances of mental state occurring without the clinical features of delirium (including isolated psychosis, catatonia, anxiety, and mania).

Our study was done with clear a-priori clinical case definitions, such as encephalitis, to support the experienced clinicians reporting cases, reflecting national guidelines, and it was clearly intended to report acute presentations. We took a strong view that the knowledge of the bedside specialist clinician assessing the patient was inherently valuable, and that rediagnosing patients from a distance would be neither wise nor accurate. Psychiatrists, for example, commonly differentiate psychosis from psychotic symptoms occurring as part of delirium; indeed, it is routine practice to provide reassurance that new-onset psychosis is actually delirium and should resolve. Even in 1918, both psychiatrists and neurologists, including Menninger and von Economo,[3] were careful to distinguish patients with primary brain dysfunction or disease from those whose symptoms were explained by systemic processes [A: Edit OK?].

Our study was designed from the outset in a three-stage approach: stage 1 is the core dataset provided by clinicians during the pandemic;[1] stage 2 is detailed clinical data collection; and stage 3 is to evaluate disease mechanisms, including viral neurotropism and para-infectious or post-infectious innate and adaptive immune responses, polygenic risk, endothelial dysfunction, and coagulopathy. Stages 2 and 3 are underway.

Substantial evidence exists that non-CNS infection can cause neuropsychiatric presentations in the absence of delirium,[4] which has now been shown with severe acute respiratory syndrome coronavirus 2 infection.[5] We therefore strongly disagree that all acute COVID-associated neuropsychiatric phenomenology can be explained by delirium. Full detailed analysis of stage 2 and 3 data from this study is underway and the multidisciplinary authors will continue to be guided by the clinical data and underlying disease mechanisms.

Altered mental status will continue to remain an important term in our global WHO and World Federation of Neurology studies of COVID-19 and the brain until these mechanisms are elucidated. We welcome ongoing discussions and collaborations on the intersections of these complex concepts and disorders as this important work progresses.

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1 Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 2020; published online June 25. https://doi.org/10.1016/S2215-0366(20)30287-X.

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4 Köhler-Forsberg O, Petersen L, Gasse C. A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. *JAMA Psychiatry* 2019; **76:** 271–79.

5 Parra A, Juanes A, Losada CP, et al. Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. *Psychiatry Res* 2020; **291:** 113254.

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